Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) selectively inhibit the reuptake of serotonin (5-hydroxytryptamine, 5-HT) in central nervous system (CNS) synapses, thus increasing the intra-synaptic concentration of serotonin.

In recent years, there has been increasing awareness of the sometimes severe withdrawal symptoms experienced by some patients. This has led to a re-evaluation of the relative risks and benefit profile of SSRIs.

Depression and serotonin

It has long been postulated that a deficiency in CNS serotonergic activity is the cause of, or a predisposing factor for, depression.[1] However, the evidence for this association is largely circumstantial and it certainly does not represent an adequate and full model for depression, probably due to there being multiple aetiological factors.[2]

Current guidance on use of SSRIs

National Institute for Health and Care Excellence guidance recommends that, in **adults**, SSRIs may be used for:[3] [4]

- Treatment of 'more severe depression' (encompassing moderate and severe depression), either alone, in combination with psychological therapy, or as a second-line option if initial psychological therapy has been ineffective, depending on the person's preferences.
- Treatment of 'less severe depression' (encompassing subthreshold and mild depression), although not as a first-line option, unless it is the person's preference.

- Treatment of generalised anxiety disorder where there is marked functional impairment, or where low-intensity psychological interventions have been ineffective.
- Treatment of moderate to severe panic disorder, if the disorder is long-standing, or if the person has declined or not benefited from psychological treatment.

The Royal College Of Psychiatrists 2019 position statement on antidepressants and depression[5] advises that:

- In moderate-severe depression, evidence-based psychological treatments should be used first-line, and antidepressants considered if:
  - The patient does not engage with treatment.
  - The patient does not respond to treatment.
  - The patient has more severe symptoms.
- Antidepressant treatment in children and adolescents should be confined to second-line treatment for moderate-to-severe depression except in exceptional circumstances. See the separate Depression in children and adolescents article for more details.
- Full information must be shared about potential level of benefits and harms, including withdrawal, and concordance about initiation and continuation.
- Discontinuation should involve tapering or slow reduction - see section on withdrawal below.

Selective serotonin reuptake inhibitors versus other antidepressants

SSRIs appear to be similar in efficacy to the older tricyclic antidepressants (TCAs) but have fewer antimuscarinic side-effects and are less cardiotoxic in overdosage.[6] SSRIs also appear to have similar clinically-significant efficacy to SNRIs, and are better-tolerated.[7] SSRIs are therefore usually the preferred first-line antidepressant class.

St John's wort (SJW) has also been compared to SSRIs. Szegedi and colleagues reported that SJW use was associated with greater depressive symptom reduction and fewer adverse effects compared with SSRIs (paroxetine).[8] However, a meta-analysis of SJW failed to find a substantial benefit over other forms of therapies.[9] It may be that SJW is safe and effective in the short-term relief of depression. SJW may be more useful in milder depression.[9] [10] NICE guidance does not recommend its use, given the uncertainties in efficacy and the potential adverse effects and drug interactions with other medications.[3]

Currently available selective serotonin reuptake inhibitors[11]

- Citalopram.
- Escitalopram.
- Fluoxetine (long half-life).
- Fluvoxamine.
- Paroxetine.
- Sertraline.
- Dapoxetine (very short half-life - licensed and used for premature ejaculation only).

Indications

- Depression - all SSRIs (except dapoxetine) are licensed for this indication; paroxetine is licensed only for the treatment of major depression.
- Panic disorder - citalopram, escitalopram, paroxetine, sertraline.
- Social anxiety disorder/social phobia - escitalopram, paroxetine.
- Bulimia nervosa - fluoxetine.
- Obsessive-compulsive disorder - fluoxetine, escitalopram, fluvoxamine, paroxetine, sertraline (the latter under specialist supervision in children).

- Post-traumatic stress disorder - paroxetine, sertraline (the latter in females only).
- Generalised anxiety disorder - paroxetine, escitalopram.
- Premenstrual syndrome (unlicensed).[12] [13]
- Premature ejaculation - SSRIs cause delayed orgasm as a side-effect, which can be useful if there is premature ejaculation. Dapoxetine, a very short-acting SSRI, is specifically licensed for this purpose, to be taken as-needed. It is expensive, however, and prescribing is often restricted or forbidden in many NHS local formularies. Other SSRIs are sometimes used, off-label.[14]

There have been a number of trials assessing the role of SSRIs as add-on therapy to improve the negative symptoms of schizophrenia. Unfortunately, a meta-analysis failed to find any difference with SSRIs.[15]

Contra-indications

Use in children and adolescents[16]

- **Antidepressants should not be prescribed except after assessment and diagnosis by a child and adolescent psychiatrist.**
- Antidepressants should not be offered to children or young people except carefully selected patients under carefully monitored conditions.
- If an antidepressant is prescribed to a child or young person, it should be fluoxetine.
- Young people and their parents or carers should be informed about the rationale, the delay in onset of effect, the time course of treatment, and the possible side-effects including the appearance of suicidal behaviour, self-harm or hostility, particularly at the beginning of treatment.
- Children should be monitored closely following initiation of antidepressant treatment; the precise frequency of monitoring should be decided on an individual basis, but NICE suggest a weekly follow-up for the first four weeks as an example regime.

- Citalopram, escitalopram, paroxetine and sertraline show an unfavourable risk:benefit balance in the treatment of depressive illness in individuals aged <18 years.
- Citalopram and sertraline should only be considered by specialists if the young person has severe symptoms which have failed to respond to other interventions.
- Paroxetine and venlafaxine (or tricyclic antidepressants) should not be used for the treatment of depression in children and young people.

Mania

SSRIs should be discontinued or avoided in patients displaying active manic symptoms; urgent psychiatry input should be sought.[17]

Cautions

- Bipolar disorder - the use of antidepressants, including SSRIs, in bipolar disorder is controversial, as they may be a trigger for mania or hypomania. Generally, if they are used, they should be used very cautiously and only alongside an effective mood stabiliser.[18] This judgement is best made by psychiatry specialists.[19]
- Epilepsy - there is the need to weigh up the risks and benefits; avoid if poorly controlled and discontinue if there is deterioration; seek specialist advice if necessary.
- Fluoxetine is reported to prolong seizure duration with concurrent electroconvulsive therapy (ECT).
- Cardiac disease - however, SSRIs (such as sertraline) are probably the safest antidepressants in cardiac disease.[20]
- Acute angle-closure glaucoma.
- Diabetes mellitus (monitor glycaemic control after initiation).
- Concomitant use with drugs that cause bleeding or gastrointestinal (GI) bleeding, or where there is history of GI bleeding.[21] [22] [3]
- Hepatic/renal impairment.

- Pregnancy and breastfeeding: seek specialist advice - eg, the National Teratology Information Service.[23] (neonatal withdrawal syndrome, particularly with paroxetine)[24] [25] Do not stop SSRIs abruptly in women who are pregnant.
- Young adults (possible increased suicide risk).[26]
- Suicidal ideation.[26]

Important interactions

- Fluoxetine, fluvoxamine and paroxetine have a higher propensity for drug interactions than other SSRIs - consider citalopram or sertraline in people who also have chronic physical health problems.[27]
- With monoamine-oxidase inhibitors (MAOIs)/moclobemide: **serious toxicity risk**. If changing from an SSRI, an MAOI or moclobemide should not be started until: five weeks after stopping fluoxetine; two weeks after stopping sertraline; one week after other SSRIs. Also, more than five weeks should elapse if on high doses or there is chronic use of fluoxetine. If changing from an MAOI, do not start SSRIs until two weeks after stopping an MAOI (but after stopping moclobemide, SSRIs can be started the following day, as moclobemide has a short duration of action).
- There is a range of interactions with a number of drugs, particularly with psychiatric medications, including other antidepressants (including St John's wort (SJW)).
- The risk of serotonin syndrome is increased by interactions with other drugs and care should be taken to monitor for its symptoms when starting new therapies in those on SSRIs. It is worth checking for known interactions of the individual SSRI with other drugs when starting new treatments.
- SSRIs inhibit platelet function and thus interact with other antiplatelet agents - eg, aspirin, clopidogrel, glycoprotein IIb/IIIa inhibitors. This interaction appears to be beneficial in acute coronary syndromes but the risk of bleeding is increased.[28]

Problems

SSRIs are generally well-tolerated, but have common side-effects.

- Minor sedation and antimuscarinic side-effects may occur but are usually less frequent and troublesome than with TCAs.
- SSRIs have relatively low toxicity in overdose. The risk of death from overdose is lower than with TCAs and venlafaxine.[27]
- GI side-effects such as nausea, vomiting, dyspepsia and constipation are quite common. Anorexia or increased appetite with weight gain may occur.
- SSRIs are associated with an increased risk of bleeding. Consider prescribing a gastroprotective drug in older people who are taking NSAIDs or aspirin or using an alternative to an SSRI.[27]
- Hypersensitivity reactions with rash may be encountered and discontinuation should be considered, as it may herald a vasculitis.
- Urticaria, angio-oedema, anaphylaxis, arthralgia, myalgia and photosensitivity may occur as idiosyncratic reactions. A range of minor CNS symptoms such as headache, insomnia, tremor and dizziness may occur.
- Hallucinations, drowsiness and convulsions have been reported (see the note on epilepsy under 'Cautions', above).
- Changes in sexual function are very common. SSRIs cause at least some degree of genital sensation change in almost everyone who takes them.[29] Common side-effects include delayed orgasm or anorgasmia. A reduced libido and reduced intensity of orgasm may also occur.[30]
    - Sexual side-effects usually resolve on cessation of SSRIs. However, relatively recently, a risk of persistent sexual dysfunction (post-SSRI sexual dysfunction, or PSSD) has been acknowledged, which may persist for decades and cause extreme distress.[29] Research into its epidemiology is extremely limited, although one recent study estimates the risk of PSSD at about 1 in 216 people taking SSRIs.[31]
- Discontinuation or withdrawal symptoms occur on cessation of SSRIs (see below).

- Hyponatraemia may occur in the elderly with SSRIs and, less commonly, with other antidepressants. It is thought to be due to the syndrome of inappropriate antidiuretic hormone (ADH) secretion. CSM advises considering the diagnosis in all elderly patients on antidepressants who develop drowsiness, confusion or convulsions. [3] [32]

- Other side-effects include sweating, galactorrhoea, urinary retention, movement disorders and dyskinesias and cutaneous bleeding (purpura and ecchymoses).

- There is a possible association between SSRI use and suicidality, although this is controversial - the main methodological limitation being the difficulty in determining whether suicidality stems from an SSRI or underlying depression. The evidence of an association seems stronger in adolescents and young people than in adults. [26] [33] [34]

- Serotonin syndrome - this can occur with overdose or concurrent MAOI use. It includes altered mental state, autonomic dysfunction, and neuromuscular abnormalities. [3] [35]

- There may also be an increased tendency of apathy in elderly individuals treated with SSRIs, despite improvement of depression. [36] Similarly, some data suggest an increase in fracture risk in patients over the age of 50 years on SSRIs. [37]

Initiation of SSRIs

- Before starting SSRIs ensure that patients are aware that they may take a few weeks to work, that they are aware of the side-effects and benefits of SSRIs, that they must stop if they develop a rash and that they must obtain help if agitation/suicidal feelings occur.

- Follow-up should be arranged after one week for young people (aged 25 or younger) and for people where there is a particular concern for risk of suicide. Otherwise, arrange follow-up within two weeks. [3]

- A trial of at least 4-8 weeks (six weeks in older patients) should be given before deciding to discontinue/change an agent.

- If there is partial response, allow another two weeks to decide if effective or not.

- There is little evidence to support the use of dose escalation in patients who do not respond to standard doses.[38]
- SSRI treatment should continue for at least 6 months after symptoms enter remission, as this reduces the risk of relapse.[3]
- Maintenance treatment may be needed in those with recurrent depression.

Withdrawal of SSRIs[3]

Stopping SSRIs leads to a withdrawal or discontinuation syndrome. Historically, the significance of this was minimalised; however, more recently, it has been recognised that this syndrome can sometimes cause severely distressing and debilitating symptoms.[39]

Typical symptoms include:

- Restlessness.
- Problems sleeping.
- Unsteadiness.
- Sweating.
- Abdominal symptoms (nausea, diarrhoea).
- Altered sensations (for example, electric shock sensations in the head - commonly called 'brain zaps').
- Altered feelings (for example, irritability, anxiety or confusion).
- Low mood.
- Suicidal ideation.
- Muscle pain and tremors.
- General malaise.

These symptoms typically occur within days of stopping the SSRI, although can occur earlier or later depending on the half-life of the drug. Fluoxetine, with a long half-life, can produce withdrawal symptoms that begin weeks after cessation.[39]

It can also be difficult to distinguish SSRI withdrawal symptoms from symptoms of a relapse of the underlying mental disorder. SSRI withdrawal symptoms usually begin sooner (within a few days of stopping) and should resolve completely within a short time if the SSRI is restarted.

Advise patients:

- Not to stop taking antidepressants suddenly; instead, discuss with a doctor first, to make a plan for how to stop.
- That it is generally better to taper the dose of an SSRI off slowly - and that most people stop taking antidepressants successfully with this.
- That SSRI withdrawal symptoms vary significantly from person to person and from drug to drug. Symptoms can range from mild, self-limiting symptoms that disappear within a few days, to severe symptoms lasting many months.

SSRIs show a hyperbolic dose-response relationship, meaning that dose reductions changes at lower doses have a larger effect on serotonin receptor occupancy.

Therefore, instead of a simple linear taper (eg, reducing the dose of sertraline from 200 mg, to 150 mg, to 100 mg, to 50 mg to zero), recent guidelines recommend a proportionate taper ie reducing the dose by a consistent proportion (eg, 25%) of the prior dose.[3] [39]

For example, a proportionate taper of citalopram - reducing the dose by 50% every 2-4 weeks - would be:[40]

- 40 mg a day, then;
- 20 mg a day, then;
- 10 mg a day, then;
- 5 mg a day, then;
- 2.5 mg a day, then;
- 1.25 mg a day, then;
- 0.6 mg a day, then stopping completely.

Tapering at very small doses is likely to require liquid rather than tablet or capsule forms of the medications.

The Royal College of Psychiatrists guidance recommends leaving at least 2-4 weeks between dose reductions, although some patients may wish to proceed slower.[40]

If discontinuation symptoms occur:

- Monitor and reassure if symptoms are mild.
- Consider re-introducing the original antidepressant or another with a longer half-life, and reduce gradually while monitoring symptoms.

Monitoring

As there is a potential risk of increased suicidal ideation in those taking SSRIs, it is a good idea to ask explicitly about these symptoms and to document them before initiating these agents, and when reviewing a patient on SSRIs.

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